SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Research Article

# Aprepitant for Nausea and Vomiting Induced by Highly and Moderately Emetogenic Chemotherapy in Japanese Patients with Gastrointestinal Cancer: A Single-Center, Retrospective Study

**Akihito Tsuji[1,2]*, Kazuma Kobayashi[2,3], Yasuhiro Hata[2,4], Yuji Negoro[2] and Sojiro Morita[4]**

[1]*Department of Medical Oncology, Kobe City Medical Center Hospital, Kobe, Japan*
[2]*Department of Medical Oncology, Kochi Health Sciences Center, Kochi, Japan*
[3]*Department of Surgery, Nagasaki University, Nagasaki, Japan*
[4]*Department of Radiology, Kochi Health Sciences Center, Kochi, Japan*

***Corresponding author**
Akihito Tsuji, Department of Medical Oncology, Kobe City Medical Center Hospital, 2-1-1, Minami-machi, Minato-jima, Chuo-ku, Kobe 650-0047, Hyogo, Japan, Tel: 81-78-302-4321; Fax: 81-78-302-7537; E-mail: tsuji@kcho.jp

**Submitted:** 16 April 2014
**Accepted:** 25 April 2014
**Published:** 06 June 2014
**ISSN:** 2333-7079



**Keywords**
- Aprepitant
- Antiemetics
- Adverse events
- Gastrointestinal cancer
- Chemotherapy-induced nausea and vomiting

**Abstract**

It is important to prevent nausea and vomiting to maintain both the quality of life of patients with cancer and the efficacy of chemotherapy. The aim of this study was to examine the efficacy of aprepitant for treatment of chemotherapy-induced nausea and vomiting (CINV) in Japanese patients with gastrointestinal cancer receiving highly or moderately emetogenic chemotherapy (HEC or MEC) regimens. A single-center, retrospective study was performed in 37 consecutive patients scheduled for HEC (n=7) or MEC (n=30). The MASCC Antiemesis Tool (MAT) was used to assess CINV and safety and patient charts were assessed before and after use of the aprepitant regimen. During the first course of chemotherapy, patients received a standard antiemetic regimen. Aprepitant was added in the second chemotherapy cycle for patients who had insufficient relief of CINV with the standard antiemetic regimen. All patients in the HEC cohort were treated with S-1 and cisplatin and those in the MEC cohort received chemotherapy including FOLFOX, FOLFIRI and irinotecan monotherapy. In patients receiving HEC, CINV symptoms tended to improve with use of aprepitant compared with antiemetic regimens without aprepitant; however, the differences were not significant. In patients receiving MEC, there were significant differences in acute and delayed nausea and vomiting with aprepitant treatment ($p<0.05$, Wilcoxon rank test). CINV symptoms improved in 70% and 78% of patients treated with HEC and MEC, respectively. These results suggest that aprepitant is effective for preventing CINV in patients with gastrointestinal cancer receiving HEC or MEC.

## ABBREVIATIONS

CINV: Chemotherapy-Induced Nausea and Vomiting; HEC: Highly Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy

## INTRODUCTION

Tumor reduction and survival of patients with cancer have been markedly improved by advances in chemotherapy with new anticancer drugs, including molecularly targeted agents and new chemotherapy regimens. In the practical setting, evidence-based treatment is important to obtain a clinical benefit, particularly in terms of the dose intensity of chemotherapy, and it is of utmost importance to determine the most appropriate dose and administration cycle for anticancer drugs. Chemotherapy-induced nausea and vomiting (CINV) is a distressing adverse

reaction for patients [1,2] and poor control of CINV may require dose reduction [3], with a consequent reduction in efficacy. Therefore, it is important to prevent nausea and vomiting to maintain both the quality of life of patients with cancer and the efficacy of chemotherapy.

Aprepitant is a selective nonpeptide neurokinin 1 ($NK_1$) receptor antagonist developed for prevention of CINV. Several randomized controlled trials have shown greater efficacy of triple combination therapy with aprepitant, serotonin 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonists and steroids for both acute and delayed CINV, compared with doublet combination therapy with $5\text{-}HT_3$ antagonists and steroids [4-8]. Aprepitant was approved in the United States and Europe between 2003 and 2005 and is currently used in more than 70 countries. It is strongly recommended as a preventive agent for acute and delayed CINV in the guidelines for antiemetic therapy published by the American Society of Clinical Oncology (ASCO) [9,10], the Multinational Association of Supportive Care in Cancer (MASCC) [11], and the National Comprehensive Cancer Network (NCCN) [12]. However, aprepitant was not launched in Japan until December 2009 (Emend Capsule; Ono Pharmaceutical, Co., Ltd., Osaka Japan). The standard antiemetic regimens available in Japan before approval of aprepitant were doublet combinations of $5\text{-}HT_3$ antagonists and steroids that were not recommended by current international antiemetic guidelines [10-12], but rather in former guidelines, such as those published by ASCO in 1999 [13]. Updated Japanese guidelines for antiemetic treatment [14] were published in May 2010, bringing consistency with international standard antiemetic therapies.

At Kochi Health Sciences Center in Kochi, Japan, aprepitant has been incorporated in most antiemetic regimens in chemotherapy since February 2010. These regimens comprise combined antiemetic therapy with aprepitant, dexamethasone and a $5\text{-}HT_3$ receptor antagonist and are hereinafter referred to as the aprepitant regimen. The objective of the present study was to investigate whether the aprepitant regimen improves control of CINV in patients receiving highly and moderately emetogenic chemotherapy (HEC and MEC) regimens for treatment of gastrointestinal (GI) cancer, in whom CINV symptoms were observed during the first chemotherapy cycle in which they were treated with a doublet antiemetic regimen of $5\text{-}HT_3$ antagonists and steroids.

## MATERIALS AND METHODS

This single-center retrospective study was conducted in the Department of Clinical Oncology, Kochi Health Sciences Center from February 2010 to August 2010. The subjects were consecutive patients who were receiving HEC and MEC regimens with the doublet antiemetic combination of 5-HT3 antagonists and steroids given during the first chemotherapy cycle, followed by addition of aprepitant during the second cycle. Detailed records of adverse events (AEs) were obtained from electronic health records to compare CINV symptoms before and after use of the aprepitant regimen. Doublet antiemetic combinations of 5-HT3 antagonists and steroids were administered in accordance with the 1999 ASCO practice guidelines for use of antiemetics in oncology [13]; granisetron 40 μg/kg or ondansetron 4 mg was used as the 5-HT3 antagonist. The aprepitant regimen was administered in accordance with the 2006 ASCO practice guidelines for use of antiemetics in oncology [9]. In the aprepitant regimen, the dose of dexamethasone was decreased by about 50% from that used in the doublet regimen due to the drug-drug interaction between aprepitant and dexamethasone (Table 1) [15]. Rescue use of 5-HT3 antagonists and/or steroids given orally or intravenously as required was permitted if symptoms occurred.

Acute (0-24 h after chemotherapy) and delayed (24-120 h) symptoms of CINV were compared before and after use of the aprepitant regimen using the MASCC Antiemesis Tool (MAT) for nausea and vomiting, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [16], and patient charts. Improvements in symptoms of emetogenicity with aprepitant were also evaluated for HEC and MEC regimens. Improvement of symptoms was defined as a decrease of at least one CTCAE grade in CINV symptoms in the cycle during which aprepitant was used compared with the cycle without aprepitant.

The study was conducted after receiving approval from the ethical review board of the hospital. Informed consent was obtained from all patients treated with the aprepitant regimen. A Wilcoxon signed-rank test was used in statistical analysis to compare CINV symptoms before and after use of the aprepitant regimen.

## RESULTS AND DISCUSSION

Thirty-seven patients were included in the study, with 7 and

**Table 1:** Schedule of antiemetic regimens.

| | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| HEC regimen | | | | |
| Conventional antiemetic regimen (cycle 1) | | | | |
| $5\text{-}HT_3$ receptor antagonist † | iv | - | - | - |
| Dexamethasone | 19.8 mg (iv) | 8 mg (po) | 8 mg (po) | 8 mg (po) |
| Aprepitant regimen | | | | |
| Aprepitant | 125 mg (po) | 80 mg (po) | 80 mg (po) | - |
| $5\text{-}HT_3$ receptor antagonist † | iv | - | - | |
| Dexamethasone | 9.9 mg (iv) | 6.6 mg (po) | 6.6 mg (po) | 6.6 mg (po) |
| MEC regimen | | | | |
| Conventional antiemetic regimen (cycle 1) | | | | |
| $5\text{-}HT_3$ receptor antagonist † | iv | - | - | - |
| Dexamethasone | 19.8 mg (iv) | 8 mg (po) ‡ | 8 mg (po) ‡ | - |
| Aprepitant regimen | | | | |
| Aprepitant | 125 mg (po) | 80 mg (po) | 80 mg (po) | - |
| $5\text{-}HT_3$ receptor antagonist † | iv | - | - | - |
| Dexamethasone | 9.9 mg (iv) | 6.6 mg (po) ‡ | 6.6 mg (po) ‡ | - |

† $5\text{-}HT_3$ receptor antagonist = granisetron 40 μg/kg or ondansetron 4 mg
‡ Dexamethasone administration on days 2 and 3 was optional
**Abbreviations:** HEC = Highly Emetogenic Chemotherapy; iv = IntraVenous; MEC = Moderately Emetogenic Chemotherapy; po = oral

**Table 2:** Patient characteristics and chemotherapy regimens.

| | HEC (n = 7) | MEC (n = 30) |
|---|---|---|
| Sex, n (%) | | |
| Male | 4 (57.1) | 23 (76.7) |
| Female | 3 (42.9) | 7 (23.3) |
| Age, mean (range), years | 55.1 (35-68) | 60.4 (33-81) |
| Cancer type, n (%) | | |
| Colorectal | 0 (0) | 20 (66.7) |
| Gastric | 7 (100) | 8 (26.7) |
| Esophageal | 0 (0) | 0 (0) |
| Pancreatic | 0 (0) | 2 (6.7) |
| Chemotherapy regimen, n (%) | | |
| S-1/cisplatin | 7 (100) | 0 (0) |
| FOLFOX | 0 (0) | 7 (23.3) |
| FOLFIRI | 0 (0) | 15 (50.0) |
| IRIS | 0 (0) | 2 (6.7) |
| Irinotecan monotherapy | 0 (0) | 1 (3.3) |
| Other | 0 (0) | 5 (16.7) |

**Abbreviations: FOLFOX** = Folinic acid, Fluorouracil, Oxaliplatin; **FOLFIRI** = Folinic acid, Fluorouracil, Irinotecan; **HEC** = Highly Emetogenic Chemotherapy; **IRIS** = Irinotecan, S-1; **MEC** = Moderately Emetogenic Chemotherapy

30 patients in the HEC and MEC cohorts, respectively. Patient characteristics and chemotherapy regimens are shown in Table 2. All patients in the HEC cohort had gastric cancer and were receiving a combination of S-1 and cisplatin. Colorectal cancer was the most common cancer type in the MEC cohort and a variety of chemotherapy regimens were used. Antiemetic therapy in the second chemotherapy cycle was given in accordance with the schedule shown in Table 1. Patients continued to be treated with aprepitant after the second cycle of chemotherapy.

Changes in the grade of nausea and vomiting before and after use of the aprepitant regimen are shown in Figures 1 and 2. The grade of CINV symptoms tended to decrease in HEC recipients (Figure 1), although the difference was not significant. In patients receiving MEC, addition of aprepitant significantly improved the grades of acute and delayed nausea and delayed vomiting (Figure 2). Symptoms were improved in 78% and 70% of patients treated with HEC and MEC, respectively.

Aprepitant was well tolerated overall. AEs considered possibly related to aprepitant were eruption of grade 1 in one patient (2.3%) and hiccups of grades 1 and 3 in three (6.9%) and one (2.3%) patients, respectively. The eruption persisted after withdrawal of aprepitant, and aprepitant was administered again with no deterioration of symptoms. The patients with hiccups did not require cessation of treatment.

These results show that an aprepitant-based regimen is effective for CINV in patients with GI cancers receiving HEC or MEC. To our knowledge, this is the first investigation of the efficacy of aprepitant in both highly and moderately emetogenic chemotherapy in Japanese patients with GI cancers, with evaluation using the MAT. CINV is a severe symptom of antineoplastic therapy and strongly influences patients' quality of life. Many antiemetic agents have been developed for prevention and treatment of CINV, and control of CINV has improved markedly since the launch of 5-$HT_3$ receptor antagonists and steroids (dexamethasone) in the 1990s. However, prevention and management of delayed CINV occurring more than 24 hours after initiation of chemotherapy remains inadequate, even if 5-$HT_3$ receptor antagonists and steroids are used. Delayed CINV occasionally leads to anticipatory CINV, which occurs before a second or subsequent course of chemotherapy, but may begin during or after administration of chemotherapy in any cycle, which compromises adherence to treatment. Furthermore, many patients with GI cancer have decreased appetite and malnutrition due to the cancer itself, and therefore the emetic risks of chemotherapy in such cases may be more severe than for patients with other cancers.

Aprepitant is a selective $NK_1$ receptor antagonist with a mechanism of action that differs from other antiemetic agents. Importantly, aprepitant has been shown to be highly effective against delayed CINV, as well as acute CINV [4-8], and is strongly recommended in international guidelines for antiemetic treatment published by ASCO [9,10], MASCC [11] and NCCN [12]. However, the use of aprepitant in clinical practice in Japan was substantially delayed compared with the United States and Europe because the drug was approved in Japan several years after approval elsewhere. Before approval of aprepitant in Japan in December 2009, clinicians had restricted antiemetic options and were unable to prescribe regimens used in other countries.

In the current study, aprepitant produced improvements in CINV symptoms compared with prior dual therapy in the majority of patients and was not associated with any severe AEs requiring treatment withdrawal. In patients receiving an HEC regimen, CINV symptoms were not significantly improved with aprepitant treatment compared with a double combination regimen given during the first course of chemotherapy. This finding may be due to the small number of patients in the HEC cohort being insufficient to achieve statistical significance, and it should be noted that all of their symptoms appeared to improve (Figure 1). In all current antiemetic guidelines, triple combination antiemetic therapy of aprepitant, 5-$HT_3$ receptor antagonists and steroids is recommended as standard therapy with HEC regimens [9-12]. Therefore, aprepitant should be used from the first cycle of chemotherapy in patients receiving HEC regimens.

Acute and delayed nausea and delayed vomiting were significantly improved in patients receiving MEC regimens. However, recommendation of aprepitant for MEC regimens is controversial [9-12]. Our results suggest that triple combination antiemetic therapy with aprepitant, 5-$HT_3$ receptor antagonists and steroids should be used in patients receiving MEC, particularly those with GI cancer. Fukazawa *et al.* [17] found that use of an aprepitant regimen led to significantly higher proportions of "no nausea" overall (days 1-5) and in the delayed (days 2-5) period compared to results obtained before approval of aprepitant for MEC regimens. The results of the current study concur with these findings and indicate that administration of aprepitant is likely to be useful for maintenance of the dose intensity and efficacy of chemotherapy.

CINV differs greatly among patients and is an AE that is difficult to confirm under actual clinical conditions, particularly in outpatients. The results of this study showed that many patients experienced delayed CINV at home. AEs such as nausea

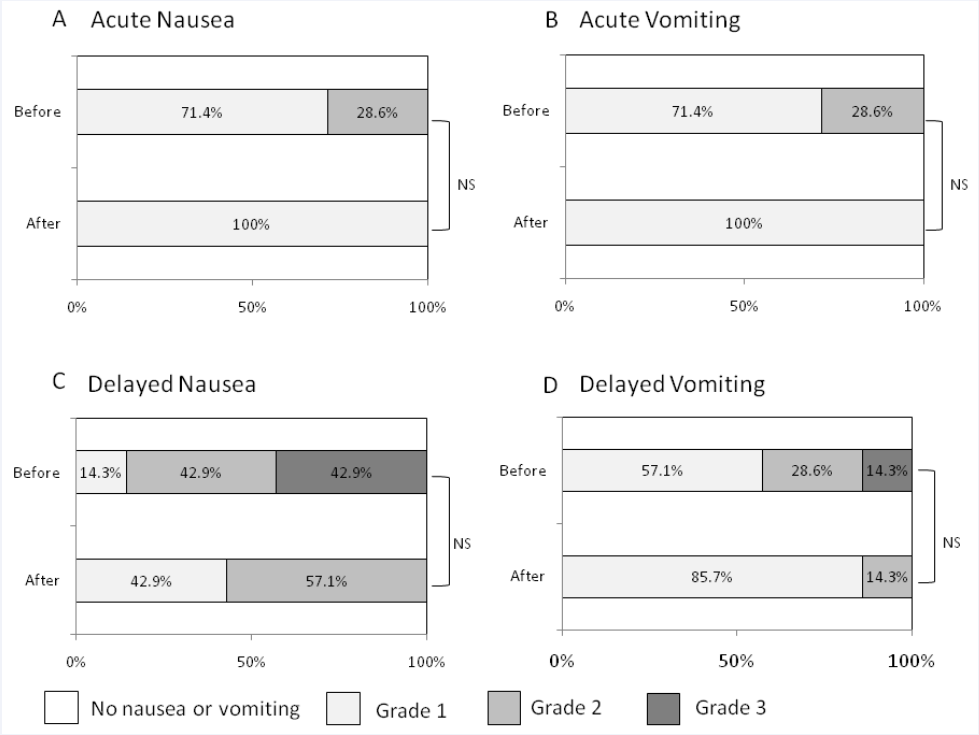


**Figure 1** Changes in symptoms of nausea and vomiting before and after administration of aprepitant in patients receiving highly emetogenic chemotherapy (HEC) regimens. Seven patients receiving HEC regimens did not receive aprepitant during the first chemotherapy cycle. The drug was added in the next cycle. Acute (a) and delayed (b) nausea, and acute (c) and delayed (d) vomiting were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. [16]. NS = not significant.

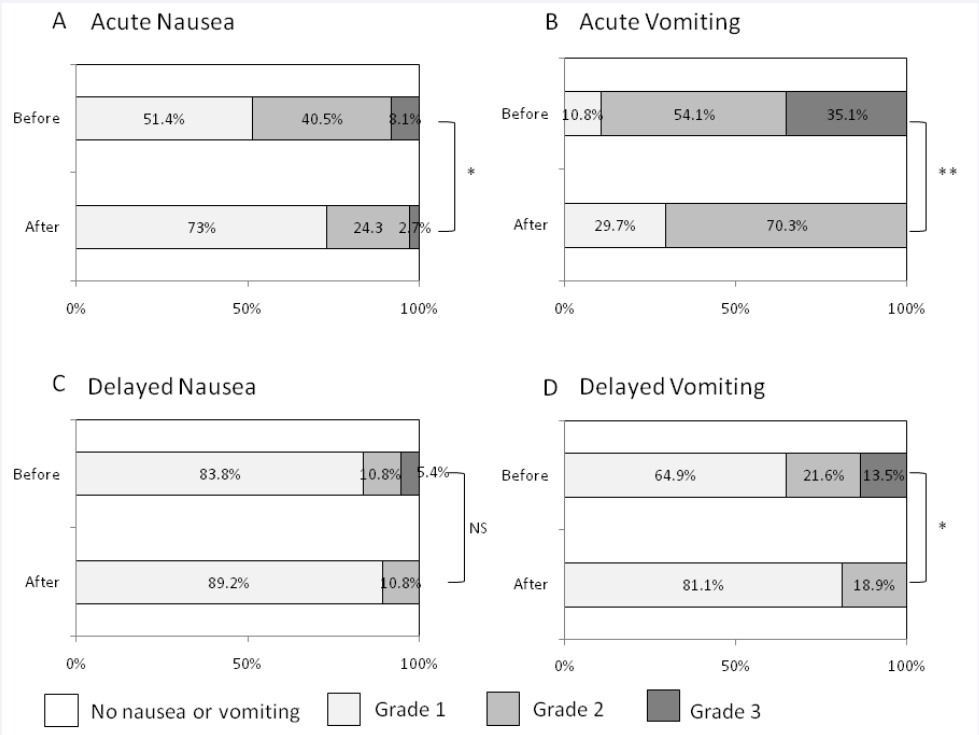


**Figure 2** Changes in symptoms of nausea and vomiting before and after administration of aprepitant in patients receiving moderately emetogenic chemotherapy (MEC) regimens. Thirty patients receiving MEC regimens did not receive aprepitant during the first chemotherapy cycle. The drug was added in the next cycle. Acute (a) and delayed (b) nausea, and acute (c) and delayed (d) vomiting were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. [16]. * $p<0.01$; ** $p<0.001$; NS = not significant.

and vomiting are under-reported and have been found to occur more frequently than confirmed by physicians [18]. This suggests that other medical staff with frequent contact with patients, such as nurses, should discuss symptoms with patients and propose measures for the management of nausea and vomiting to enhance the assessment of AEs.

This study has several limitations. First, it was conducted retrospectively without a control arm, and further prospective comparative research will therefore be needed, especially with respect to the first cycle of MEC regimens. Second, CINV symptoms were compared in the same patients before and after using aprepitant; however, the efficacy of aprepitant might have been influenced by previous chemotherapy. Third, approximately 30% of patients stated that "I did not feel any improvement", which suggests that the 5-day administration period of aprepitant should be evaluated and that combination with the 5-$HT_3$ receptor antagonist palonosetron (which has been found to be effective for delayed nausea and vomiting [19]) should be considered to improve the antiemetic effects. Finally, the sample size was too small, especially the HEC cohort, to draw definitive conclusions from the current results alone.

## CONCLUSION

The aprepitant regimen used in the study had a strong antiemetic effect for both HEC and MEC. The positive results are indicative of the efficacy of aprepitant, given the nature of the chemotherapy regimens and the risk factors for patients with GI cancer. Thus, the results of this study suggest that aprepitant is effective for prevention of CINV in highly and moderately emetogenic chemotherapy in Japanese patients with GI cancers.

## REFERENCES

1. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, et al. On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol. 1983; 19: 203-208.

2. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, v Beurden V, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer. 1997; 76: 1055-1061.

3. Neymark N, Crott R. Impact of emesis on clinical and economic outcomes of cancer therapy with highly emetogenic chemotherapy regimens: a retrospective analysis of three clinical trials. Support Care Cancer. 2005; 13: 812-818.

4. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin: The Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003; 21: 4112-4119.

5. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer. 2003; 97: 3090-3098.

6. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol. 2005; 23: 2822-2830.

7. Takahashi T, Hoshi E, Takagi M, Katsumata N, Kawahara M, Eguchi K. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. Cancer Sci. 2010; 101: 2455-2461.

8. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. 2010; 18: 423-431.

9. American Society of Clinical Oncology, Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol. 2006; 24: 2932-2947.

10. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29: 4189-4198.

11. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010; 21 Suppl 5: v232-243.

12. National Comprehensive Cancer Network. (2014) NCCN Clinical Practice Guidelines in Oncology. Antiemesis v.1.2014.

13. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol. 1999; 17: 2971-2994.

14. The Japan Society of Clinical Oncology. Guidelines for Appropriate Treatment with Antiemetics. 1st Version, Kanehara& Co., Ltd., Tokyo, 2010.

15. McCrea JB, Majumdar AK, Goldberg MR, Iwamoto M, Gargano C, Panebianco DL, et al. Effects of the neurokinin 1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther. 2003; 74: 17-24.

16. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Ver. 4.0. Japanese Edition Translated by the Japan Clinical Oncology Group (JCOG), 2009.

17. Fukazawa K, Nakazawa A, Matsuura M, Kogure N, Hirai E, Aihara R, et al. Preventive effect of aprepitant, an oral NK1 receptor antagonist, on acute and delayed chemotherapy-induced nausea and vomiting for colorectal cancer. Gan to Kagaku Ryoho (Jpn J Cancer Chemother) 2011; 38: 399-404. (in Japanese with English abstract)

18. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer. 2004; 100: 2261-2268.

19. Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol. 2009; 10: 115-124.

**Cite this article**

*Tsuji A, Kobayashi K, Hata Y, Negoro Y, Morita S (2014) Aprepitant for Nausea and Vomiting Induced by Highly and Moderately Emetogenic Chemotherapy in Japanese Patients with Gastrointestinal Cancer: A Single-Center, Retrospective Study. J Pharmacol Clin Toxicol 2(2):1030.*